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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/630,227
Filing Date: July 30, 2003
Appellant(s): DIMAURO ET AL.

Deirdre E. Sanders
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3 December 2007 appealing from the Office action mailed 27 June 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

It is noted that Appellants have exercised their right to appeal even though there has been no final rejection.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is not correct; see below:

The following grounds of rejection are not presented for review on appeal because these grounds have been withdrawn:

The rejection of Claim 1 and 89 under 35 U.S.C. § 103(a) as being obvious over Dunn (EP 1 153 606) in view of Braun et al (2003. Expert Opin. Bio. Ther 3:141-168) is not appealable because the claims have not been twice rejected on these grounds.

Upon further consideration, the rejection of claims 38 and 48 under U.S.C. § 112, 1st and 2nd paragraph is withdrawn.

The rejection of Claim 49 under 35 U.S.C. § 112, 1st paragraph as failing to comply with the written description requirement is withdrawn in view of Appellants' persuasive arguments.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Lehman et al. 2002. "Thalidomide Therapy for Recalcitrant Systemic Onset Juvenile Rheumatoid Arthritis, " J. Pediatrics. 140:125-127

Dunn. EP 1 153 607

Pike et al. US Publication No. 20030134792

Molloy et al. 2003. " The Roles of Growth Factors in Tendon and Ligament Healing," Sports Medicine 33:381-394

Smith et al. US Publication No. 20020169162

Cardone et al. 2003. "Diagnostic and Therapeutic Injection of the Hip and Knee" American Family Physician 67:2147-2152

La Van et al. 2003. "Small Scale Systems for In Vivo Drug Delivery" Nature, Biotechnology 21:1184-1191

5,194,596 Tischer et al. 3-1993

Benjamin et al. 1998. "A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF." Development 125:1591-1598

Vukicevic et al. 1996. "Induction of nephrogenic mesencyme by osteogenic protein 1 (bone morphogenetic protein 7) PNAS 93:9021-9026

Sampaio et al. 1991. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. J Exp Med. 173:699-703

Muller, GW et al. Biorganic and Medicinal Chem Lett 1999. "Amino-substituted thalidomide analogues: Potent Inhibitors of TNF-alpha production." 9:1625-1630

Teo SK. 2005. "Properties of thalidomide and its analogues: implications for cancer therapy AAPS Journal 7:E14-9

Moreira, et al. 1993. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. J Exp Med. 177:1675-1680

http://arthritis.about.com/od/kneetreatments/g/viscosupplement, downloaded 12/9/05

(9) Grounds of Rejection

Claim Interpretation

Claim 38 recites "wherein the inhibitor of TNF-α synthesis is present in the formulation in an amount of at least 100 mg/ml"; claim 48 recites "wherein the inhibitor of TNF-α synthesis is present in the formulation in a maximum amount of 0.5mg. Claim 1, the independent claim of the instant invention, from which Claims 38 and 48 depend, recite administration of an effective amount of an inhibitor of TNF-α synthesis. Appellants disclose a myriad of compounds "such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g, pentoxifylline and rolipram), A2b adenosine receptor agonists and A2b adenosine receptor enhancers" as inhibitors of TNF-α synthesis and/or activity. The disclosure comprises a non-limiting list and include compounds of vastly different chemical structures, functions, size and molecular weights. In the absence of a specific recited structure, the recitation of a specific dosage is

meaningless, as one of ordinary skill in the art would be unable to determine if the recited dosage comprises "an effective amount". Thus, the limits of these two claims cannot be given significant weight.

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 34, 37, 47, 49, 51, 54 and 56 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Dunn (2001, EP 1 153 607).

Lehman et al report two case studies of children with systemic onset rheumatoid arthritis and teach the use of thalidomide therapy for recalcitrant systemic onset juvenile arthritis (page 125, 3rd column, 1st paragraph). The patients suffering from rheumatoid arthritis had arthritis in the knees (page 125, column 3, 2nd paragraph and page 126, column 1, three lines from the bottom of page), thus suffering from inflammation of the

knee joints which comprise all of the structural elements recited in claim 1. The patients were systemically treated with thalidomide (page 126, 1st column, 1st paragraph and page 126, 2nd column 1st paragraph). The reference is silent as to the specific method of systemic administration; however the reference teaches administration of other therapeutic compounds intravenously (page 125, 2nd column). Lehman et al disclose that thalidomide enhances the degradation of TNF-α mRNA (page 125, column 3, last paragraph); one of ordinary skill in the art would recognize that a compound which enhances messenger RNA degradation would thereby inhibit the synthesis of TNF-α.

Lehman does not teach transcapsular administration of the formulation into the knee joint, the transcapsular administration a formulation comprising at least one additional growth factor, the administration of a formulation in an amount of less than 1 cc, the administration of the formulation closely adjacent to the outer wall of the capsule, the administration of a growth factor in an amount effective to repair joint tissue, the administration of a formulation that includes a viscosupplement or the administration performed through a needle.

Dunn (EP 1 153 607) teaches the injection of a mixture of purified growth hormone and buffer solution into a joint (abstract, page 1) to treat inflammation of the joint, and specifically discloses treatment of a knee joint (column 1, paragraph 0001, lines 5-7). The reference teaches a preliminary step comprising injection of a group of agents such as anti-cytokines (column 3, paragraph 0008, lines 45-47), which would by definition include an inhibitor of TNF- α synthesis. The reference teaches treatment of the joint with "a group of agents such as anti-cytokines, …..so as to reduce or remove deleterious activity in the joint" (column 3, 0009, lines 38-44); one of anti-cytokines envisioned is Embrel, an anti-TNF antibody. Dunn discloses that a preferred volume is generally between 0.5 to 10 milliliters (column 8, paragraph 0029, lines 39-40) and that the formulation is injected utilizing a syringe into the joint space (trans-capsular administration) and not directly into the bone or tissue (column 7, paragraph 0027, lines 30-32, and figure 2). The reference teaches that the invention may additionally comprise the use of a lubricant or viscosupplement such as purified hyaluronic acid or

hyaluronate salt (column 9, paragraph 0032, lines 25-28). Viscosupplementation is defined as a "procedure that involves the injection of gel-like substances (hyaluronates) into a joint to supplement viscous properties of a synovial fluid" (see, for teaching purposes only,http://arthritis.about.com/od/kneetreatments/g/viscosupplement, downloaded 12/9/05). Dunn teaches the administration of a dose of growth hormone as a means of regenerating articular cartilage in the joint, thus achieving repair of joint tissue.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the administration of the formulation comprising thalidomide taught by Lehman using the administration route, direct administration to the knee joint space, taught by Dunn. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide and Dunn discloses a step involving treatment of the joint with "a group of agents such as anti-cytokines, …..so as to reduce or remove deleterious activity in the joint" (column 3, 0009, lines 38-44); one of anti-cytokines envisioned is Embrel, an anti-TNF antibody. This would comprise administering an inhibitor of TNF activity. The skilled artisan reasonably would have expected success because Dunn discloses the injection of formulations into the joint to treat joint inflammation (page 1, abstract). Additionally, one of skill in the art would have been motivated to modify the route of administration and would have expected success because administration of therapeutic agents by alternative routes of administration is well known in the art.

Claims 36, 39-43, 45, 58, 60, 61, 63-65 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Pike et al (US PUB 20030134792)

The teachings of Lehman et al. and the relevance of said teachings to the instant invention are disclosed in detail above. Lehman et al do not disclose a formulation further comprising liposomes, a sustained, controlled release device, providing

continuous release, or intermittent release, a hydrogel, a formulation administered in a volume of between 0.03 and 0.3 ml (30-300 µl), a formulation in a patch attached to an outer wall of the capsule, a formulation in a depot closely adjacent an outer wall of the capsule, the release of the antagonist by diffusion through a sustained delivery device, a polymer sustained delivery device, microspheres having a plurality of degradation rates or wherein the antagonist is released by biodegradation of a sustained delivery device.

Pike et al disclose a method for treating articular cartilage disorders, such as osteoarthritis of the knee, by administering IGF-1at the diseased or injured articular site (paragraph 0014). Such administration may be achieved directly at the site, as with intra-articular injection (paragraph 0021). Such intra-articular injections to the knee joint comprise injection directly into the joint space of the osteoarhritic knee joint (transcapsular administration). The reference teaches additional methods of administration of therapeutic composition into the capsule of the diseased joint. Among the methods of administration taught are: a sustained release device (paragraphs 0053 and 0059), which would, by definition, comprise a controlled release device providing continuous release. The reference teaches that the device may be implanted within the diseased or injured joint (paragraph 0053), which, given the broadest reasonable interpretation of the claims, would encompass attachment to the outer wall of the capsule, or a depot closely adjacent to an outer wall of the capsule. As “a patch attached to the outer wall of the capsule” is not specifically defined or described in the specification of the instant invention, a device implanted within the diseased joint could be interpreted as a patch attached to an outer wall of the capsule as, given the small size of the capsule, the device would most likely be touching the outer wall of the capsule. Pike et al teach the formulation may be enclosed in a semipermeable matrix of hydrophobic polymers (paragraph 0044), which would allow for diffusion for the high specificity antagonist through a sustained delivery system (paragraph 0044). The reference teaches the use of hydrogels and microcapsules (microspheres) (paragraph 0044) made of different materials, which would inherently have a plurality of degradation

rates and comprise a device which provides intermittent release (paragraph 0044). Pike et al also teach that sustained release forms could include colloidal drug delivery systems such as liposomes (paragraph 0044). Pike et al teach administration of a pharmaceutical composition in a volume ranging from 100 µl to about 5 ml (paragraph 0047). The pharmaceutical formulation taught by Pike et al may comprise other therapeutic agents, including anti-inflammatory agents (paragraph 0038).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the systemic administration comprising thalidomide, an inhibitor of the production of the cytokine TNF-α, as taught by Lehman, and deliver the drug directly (locally) to diseased or injured articular site, including knee joint (trans-capsular administration), using the direct delivery systems disclosed by Pike et al. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide, and US PG PUB 2003/0134792 teaches that the pharmaceutical composition of the disclosed invention may comprise one or more other therapeutic agents including but not limited to anti-inflammatory agents (paragraph 0038), which would encompass agents that inhibit TNF-α synthesis and activity. The skilled artisan reasonably would have expected success because Pike et al. teach that sustained release devices are well known in the art (paragraph 0053). Additionally, one of skill in the art would have been motivated to make this modification and would have expected success because administration of therapeutic agents by alternative routes of administration is well known in the art.

Claim 50 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) and Dunn (EP 1 153 606) as applied to Claims 1 and 49 further in view of Molloy et al. (2003. Sports Med. 33:381-394).

The teachings of Lehman et al., and Dunn and the relevance of these teachings to the instant Appeal Brief are disclosed in detail above. Lehman et al. and Dunn do not teach the specific use of a formulation comprising a growth factor provided by platelet

concentrate. However, Dunn does teach injection of growth factor into the knee joint for treatment of joint inflammation.

The specification teaches that the growth factors that may be used in accordance with the present invention include members of the platelet-derived growth factor (PDGF) family [paragraph 0195 of PGPUB 20050025765, the PGPUB of the instant invention]. The art recognizes that Platelet Derived Growth Factor was originally purified from platelets and is released from activated platelets. The specification teaches platelet concentrate recited in Claim 50 comprises the growth factors released by the platelets [paragraph 0197]; thus, the platelet derived growth factor, as taught by Molloy et al would by definition, be a growth factor derived from platelet concentrate (as recited in Claim 50).

Molloy et al teach that platelet-derived growth factor (PDGF) plays a significant role in early stages of healing of all tendons, both intrasynovial and extrasynovial (page 383, column 1, 1st paragraph and page 387, Column 1, Section 1.4, paragraph 1). Injury to an intrasynovial tendon would, by definition, result in an inflamed orthopedic joint. The reference teaches that the introduction of PDGF into the injury site of healing rabbit femur-MCL-tibia complexes, the knee joint area, increases the quality of healing (page 390, column 1, paragraph 2 and Table III). Introduction of PDGF to this area would comprise introduction of PDGF to the area of the injured (inflamed) knee joint.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify a formulation comprising thalidomide, as taught by Lehman by adding a growth factor such as PDGF as suggested by Dunn and Molloy et al and administer said formulation into the joint space (transcapsular administration) as taught by Dunn. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide, and Dunn teaches delivery of therapeutic compositions directly to the joint and that said therapeutic composition may comprise one or more additional therapeutic agents including but not limited to anti-inflammatory agents or growth factors and Molloy et al. teach that PDGF has vital functions during

early and intermediate stages of healing (page 391, column 2, 2nd paragraph). The skilled artisan reasonably would have expected success because Molloy et al. teach that growth factors have vital functions during early and intermediate stages of healing (page 391, column 2, 2nd paragraph) and Dunn teaches administration of pharmaceutical composition said pharmaceutical compositions may comprise one or more therapeutic agents including but not limited to anti-inflammatory agents and growth factors. Additionally, one of skill in the art would have been motivated to make this modification and would have expected success because administration of therapeutic agents by alternative routes of administration is well known in the art.

Claims 1, 53 and 57 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Smith et al. (2002, PG PUB US 2002/0169162).

The teachings of Lehman et al. and the relevance of these teachings to the instant Appeal Brief are disclosed in detail above. Lehman does not disclose the injection of the formulation into the synovial fluid or the administration of the formulation through a drug pump.

Smith et al teach an implantable sustained release device for locally administering a therapeutically effective compound to a joint (paragraph 0017), including a knee joint (paragraph 0070); ie injecting therapeutic agents into the knee joint. The device is a mechanical one, implanted intraarticularly to deliver a therapeutically effective compound within a synovial capsule of the joint (abstract). Thus, the reference teaches administration of a therapeutically effective compound to the synovial fluid of a joint (paragraph 0041).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to administer a formulation comprising thalidomide as taught by Lehman et al. using the pump device disclosed by Smith et al. The person of ordinary skill in the art would have been motivated to make that modification because

the art recognizes the toxic side effects of the systemic use of thalidomide and US PG PUB 2002/0169162 teaches that the device could be used to release drugs over an extended period of time in a controlled fashion. Among the drugs to be administered by the device taught by Smith et al. are anti-inflammatory drugs (paragraph 0044). The art recognizes that TNF-α plays a major role in the development of inflammation; thus thalidomide, which inhibits TNF-α synthesis is encompassed by the definition of anti-inflammatory drugs. The skilled artisan reasonably would have expected success because Smith et al. teach the advantages achieved by an implantable sustained release device for locally administering a therapeutically effective compound to a joint (paragraph 0017). Moreover, administration of therapeutic agents by alternative routes of administration is well known in the art.

Claim 55 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) and Dunn as applied to Claim 1 in view of Cardone et al (2003, American Family Physician, 67:2147-2152).

The teachings of Lehman et al. and Dunn and the relevance of these teachings to the instant Appeal Brief are disclosed in detail above. Lehman et al. and Dunn do not disclose removing a portion of synovial fluid prior to administration of the antagonist.

Cardone et al teach a method of removing fluid from the knee joint by aspiration (page 2147, abstract, page 2151, column 2, 2nd paragraph) to aid in diagnosis and relieve discomfort. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administration of thalidomide as taught by Lehman et al. and Dunn (administration directly to the inflamed knee joint) by aspirating fluid from the knee joint prior to administration as taught by Cardone et al. The person of ordinary skill in the art would have been motivated to make that modification because Cardone et al teach that aspiration may be performed to aid in diagnosis and relieve discomfort and one would always be motivated to relieve discomfort. Additionally, one would be motivated to remove fluid from the inflamed knee joint so as not to increase fluid pressure in the knee joint when administering a

therapeutic compound. The skilled artisan reasonably would have expected success because Cardone et al. teach detailed technique for performing this procedure (entire paper).

Claim Rejections-35 U.S.C. § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 46, which depends from claims 1 and 39 is directed to a method of administration wherein the formulation comprises a sustained release device, wherein the sustained release device comprises an inflammatory-responsive delivery system. The claim is interpreted as reciting a device which senses the presence of inflammation in the joint, and then releases a therapeutic formulation in response to said inflammation. Thus, if the degree of inflammation in the joint increases, the device will release an increased amount of the therapeutic formulation; if the inflammation subsides, the device will cease the release of the therapeutic formulation.

There are no teachings in the specification nor are there any examples, working or prophetic, directed to the use of such an “inflammatory-responsive delivery system”.

The teachings in the art do not remedy this lack of guidance in the disclosure. The art teaches (LaVan et al 2003, Nature Biotechnology 21:1184-1189) that a limiting step in the creation of responsive drug delivery systems has been the development of stable sensors (page 1189, column 1, 2nd paragraph). The reference, by way of example, teaches the most mature technology in development of such systems is that directed to integration of drug delivery with systems to sense blood glucose levels and release of insulin in response. La Van et al teach that "no fully automatic long-term *in vivo* system has been brought to market because of stability problems with *in vivo* glucose sensors" (page 1189, column 1, 2nd paragraph). It would require undue experimentation by the skilled artisan to determine what inflammatory signal the delivery system would respond to, and to develop a sustained release delivery system that would deliver a therapeutic agent to the joint in response to said inflammatory system.

Claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 49 is drawn to a method of treatment comprising administration into the joint space an effective amount of an inhibitor of TNF-α synthesis wherein the formulation further comprises a growth factor present in an amount effective to repair joint tissue.

The specification defines the term "growth factors" very broadly. Growth factors encompass "any cellular product that modulates the growth or differentiation of other cells". ….. The growth factors that may be used in accordance with the present invention include, but are not limited to, members of the fibroblast growth factor family, including acidic and basic fibroblast growth factor (FGF-1 and FGF-2) and FGF-4, members of the platelet-derived growth factor (PDGF) family, including PDGF-AB, PDGF-BB and PDGF-AA; EGFs; the TGF-.beta superfamily, including TGF-.beta.1, 2 and 3; osteoid-inducing factor (OIF); angiogenin(s); endothelins; hepatocyte growth

factor and keratinocyte growth factor; members of the bone morphogenetic proteins (BMP's) BMP-1, BMP-3, BMP-2; OP-1, BMP-2A, BMP-2B, and BMP-7; HBGF-1 and HBGF-2; growth differentiation factors (GDF's); members of the hedgehog family of proteins, including indian, sonic and desert hedgehog; ADMP-1; other members of the interleukin (IL) family; and members of the colony-stimulating factor (CSF) family, including CSF-1, G-CSF, and GM-CSF, and isoforms thereof; and VEGF." [Paragraph 0195 of PGPUB of the instant invention]. Thus, Appellants have listed many different families of growth factors, each comprising a number of member proteins. The specification teaches and the art recognizes many members of the BMP family of proteins, each with unique morphogenic effects. There are also numerous GDFs considered to be a subset of BMP family of proteins.

However, the teachings in the specification are not limiting, and there is no guidance as to which of the myriad growth factors, some of which have opposite effects, would be effective to repair joint tissue.

There are no examples, working or prophetic, teaching the use of any formulations comprising inhibitors TNF-α synthesis and growth factors in the methods of the instant invention.

The art teaches: The relevant literature reports examples of polypeptide families of growth factors wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS

USA 93:9021-9026) disclose that OP-1, a bone morphogenic protein that is a member of the TGF-family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-family members BMP-2 and TGF- 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). Thus, one of skill in the art would not be able to predict which, if any, growth factors would be "effective to repair joint tissue". Administration of said listed growth factors to repair joint tissue is not routinely practiced in the art. In the absence of teachings in the specification or working examples, Appellants' recitation is an invitation to experiment to determine which of the myriad growth factors would be effective to repair joint tissue. It would require undue experimentation on the part of the skilled practitioner which of the growth factors, which are known to have distinct, and often opposite effects, would be effective to repair joint tissue.

Due to the large quantity of experimentation necessary to determine which member of a given growth factor family would have the required activity of repairing joint tissue, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based membership in a given protein family, and the breadth of the claims which embrace a broad class of protein families, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(10) Response to Arguments

The rejection of Claims 1, 2, 34, 37, 47, 49, 51, 54 and 56 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Dunn (2001, EP 1 153 607).

At page 8, 2nd full paragraph of the Appeal Brief, Appellants argue that Lehman et al. teach thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α; Lehman et al cite a reference, in discussion section (Gori et al. 2000. J Infect

Dis. 182:639-640, reporting an increase in TNF-α production following thalidomide treatment in a population of HIV and M. tuberculosis-infected patients) that suggests thalidomide is not a systemic TNF-α inhibitor (page 8, 3rd paragraph of Appeal Brief). Appellants dispute examiner's statement that the specification of the instant invention teaches thalidomide among the compounds which prevent and/or inhibit TNF synthesis: "what the specification actually discloses is that TNF antagonists include 'compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide...."' (page 8, last paragraph of Appeal Brief bridging page 9, 1st paragraph). Therefore, Appellants argue that Lehman does not teach or suggest administration via trans-capsular injection and does not teach or suggest treating an inflamed orthopedic joint with an inhibitor of TNF-α synthesis and does not provide a reasonable expectation of successfully treating an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis (page 9, 1st complete paragraph of Appeal Brief). .

Appellants argue that Dunn teaches treatment of an inflamed joint by administration of growth hormone to joint space and that agents such as anti-cytokines can be injected into joint prior to, or simultaneously with the step of injecting a growth hormone and buffer solution into the joint space (page 9, 2nd and 3rd paragraph of Appeal Brief) and does not describe or suggest methods of administration of an inhibitor of TNF-α synthesis.

Appellants assert that at the time of invention, one of skill in the art would not be motivated to substitute an inhibitor of TNF-α synthesis for the growth factor in Dunn to transcapsularly administer an inhibitor of TNF-α synthesis. Appellants argue, that at the time of the instant invention, a published application teaches in its examples, that TNF inhibitors are to be administered through systemic pathways (page 10, 3rd full paragraph of Appeal Brief).

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons.

The Examiner does not disagree with appellants that Lehman does not teach or suggest administration via trans-capsular injection and Dunn does not describe or

suggest methods of administration of an inhibitor of TNF-α synthesis. Appellants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091,

Lehman et al. teach the use of thalidomide therapy for a disease known to involve inflammation of the knee joints. Lehman et al disclose that thalidomide enhances the degradation of TNF-α mRNA and was effective because of several factors, including effects on TNF-α (page 126, column 3, last paragraph). Appellants' specification teaches thalidomide is among compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, [paragraph 0096 of PGPUB 20050025765, the PGPUB of the instant invention]. Contrary to Appellants assertion, the plain meaning of the disclosure (TNF antagonists include 'compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide....) is that thalidomide is an agent which inhibits TNF synthesis. Appellants assert that the citation by Lehman et al in the discussion section (of a reference suggesting thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α activity) teaches away from treatment with an inhibitor of TNF-α inhibitor. However, the discussion of Lehman et al, concludes that thalidomide "enhances the degradation of TNF-α mRNA, thereby reducing the half life of TNF-α". This conclusion is supported by the preponderance of the art, which teaches thalidomide selectively inhibits TNF-α syntheses (Sampaio et al. 1991. J Exp Med. 173:699-703, abstract; 1999. Muller, GW et al. Biorganic and Medicinal Chem Lett 9:1625-1630, page 1625, 2nd paragraph; 2005. Teo SK. AAPS Journal 7:Article 3, abstract); this inhibition of TNF-α synthesis is most likely due to enhancement of mRNA degradation [1993. Moreira, et al. J Exp Med. 177:1675-1680, page 1678, Figure 4]). Additionally, Appellants' disclosure teaches thalidomide as an inhibitor of TNF-α synthesis and activity. While thalidomide, under special circumstances, may increase TNF-α synthesis, the preponderance of the evidence leads one of ordinary skill in the art to conclude that thalidomide enhances the degradation of TNF-α mRNA, thereby inhibiting

TNF-α synthesis. Thus, the teachings of Lehman et al. are clearly directed to administration of an inhibitor of TNF-α synthesis to treat an inflamed joint, the knee joint.

Dunn teaches treatment of an inflamed joint by administration of growth hormone to joint cavity to lessen the inflammation of the synovial lining, joint capsule, ligaments and articular cartilage. Appellants argue that the method of the instant invention is distinct from that of Dunn's (page 9 of Appeal Brief, 2nd full paragraph), citing Dunn's speculative statement as to the fate of the fluid in the injection and indicating that the goal of Dunn's therapeutic injection is different from that of the claimed invention. Appellants' arguments are not deemed persuasive. One of ordinary skill in the art would understand that the method of administration taught by Dunn is the same as Appellants' method of transcapsular administration into the joint space (joint space being the equivalent of joint cavity). Thus, Dunn teaches transcapsular administration of a therapeutic compound, which is all that is required by the limitations of the claim. What happens once the therapeutic compound is administered, and the mechanism by which said compound achieves a therapeutic effect is immaterial.

Appellants argue (page 10 of Appeal Brief, 1st full paragraph) that one of skill in the art would not be motivated to substitute an inhibitor of TNF-α synthesis for the growth factor in Dunn and administer said inhibitor to trans-capsularly on the basis of the teachings of Lehman et al of systemic administration of thalidomide. Appellants' arguments have been fully considered but are not found to be persuasive. Dunn teaches administration of agents such as anti-cytokines into joint space (capsule) prior to, or simultaneously with the step of injecting a growth hormone and buffer solution into the joint space (column 8, paragraph 0030, lines 43-56). One anti-cytokine taught by Dunn is Embrel, an anti-TNF antibody. Thus, while Dunn does not teach administration of an inhibitor of TNF synthesis, the reference teaches administration of an inhibitor of TNF activity. It would be obvious to one of ordinary skill in the art to modify the teachings of Lehman et al (of systemic administration of thalidomide) and administer the inhibitor of TNF activity (thalidomide) by direct administration to the knee joint space (transcapsular administration) as taught by Dunn. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the

toxic side effects of the systemic use of thalidomide, the art recognizes cytokines such as TNF-α, are synthesized and are active locally, not systemically, and Dunn discloses a step involving treatment of the joint with Embrel, an anti-TNF antibody (inhibitor of TNF activity).

Appellants' argue (page 10 of Appeal Brief, 2nd full paragraph) that at the time of the instant invention, one of skill in the art would not be motivated to locally administer any inhibitor of TNF-α synthesis. The state of the art was not to administer such compounds locally. At the time of the instant invention, one published application teaches in its examples, that TNF inhibitors are to be administered through systemic pathways.

Appellants' arguments have been carefully considered and have not been deemed persuasive. Examiner does not disagree, that at the time of instant invention, the art did not teach trans-capsular administration of inhibitors of TNF-α synthesis; therefore, there are no rejections under 35 U.S.C. 102. It is noted that although one reference teaches systemic administration of TNF inhibitors, Dunn, at the time of Appellants invention, teaches local administration of an inhibitor of TNF-α activity; thus Dunn provides the suggestion to administer inhibitors of TNF-α activity directly to the joint to treat inflammation. One of ordinary skill in the art would understand that inhibitors of TNF-α activity would encompass inhibitors of TNF-α synthesis including thalidomide; one would also recognize that with a drug such as thalidomide, such local administration would be highly desirable as opposed to systemic administration. Furthermore, one of ordinary skill in the art, aware that cytokines are synthesized and act locally, would understand that local administration to the site of inflammation would be more efficacious than systemic administration. Therefore, one would be motivated to combine the teachings of Lehman et al and Dunn and administer an inhibitor of TNF-α synthesis (thalidomide) directly to the inflamed orthopedic joint (transcapsular administration).

The rejection of Claims 1, 2, 34, 37, 47, 49, 51, 54 and 56 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al in view of Dunn (2001, EP 1 153 607) should be sustained for reasons set forth above.

The rejection of Claims 36, 39-43, 45, 58, 60, 61, 63-65 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Pike et al (US PUB 20030134792)

On page 11, 1st full paragraph of Appeal Brief, Appellants assert Lehman does not teach or suggest administration via transcapsular injection of an inflamed orthopedic joint with an inhibitor of TNF-α synthesis, nor does it teach the different aspects of administration disclosed in the rejected claims. Although Pike et al. teaches additional agents such as anti-inflammatory agents can be included in its composition, Pike et al does not teach or suggest administering an inhibitor of TNF-α synthesis. Thus neither reference describes or suggests Appellants' invention and do not provide a reasonable expectation of treating an inflamed orthopedic joint by trans-capsularly administering an inhibitor of TNF-α synthesis.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons.

The Examiner does not disagree with appellants that Lehman does not teach or suggest administration via trans-capsular injection and Pike et al does not teach or suggest administering an inhibitor of TNF-α synthesis. Appellants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091,

The teachings of Lehman et al. and the relevance of these teachings in response to the instant Appeal Brief are disclosed in detail above. As discussed above, Lehman et al teaches systemic administration of an inhibitor of TNF-α synthesis to treat an inflamed orthopedic joint. Pike et al teach multiple methods of administration of a therapeutic agent, IGF-1, to treat inflamed joints, including osteoarthritis and trauma-related injuries. Pike also teaches that additional therapeutic agents may be included in the formulation; examples of such agents include but are not limited to anti-inflammatory agents. The art recognizes that TNF-α is a major factor in promoting inflammation.

Thus, an agent which inhibits TNF-α synthesis and/or activity would be recognized as an anti-inflammatory agent.

In response to appellants argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Pike teaches application of therapeutic formulations intra-articularly, that is directly to the knee joint or transcapsular administration. The formulations comprise pharmaceutical compositions of anti-inflammatory agents. Lehman teaches thalidomide as one such anti-inflammatory agent, in that it enhances degradation of TNF-α mRNA, thus inhibiting synthesis of the TNF-α protein. One would have anticipated success because the Pike reference teaches multiple ways of administration of such therapeutic agents directly to the diseased joint.

The rejection of Claims 36, 39-43, 45, 58, 60, 61, 63-65 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al in view of Pike et al should be sustained for reasons set forth above.

The rejection of Claim 50 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) and Dunn (EP 1 153 606) as applied to Claims 1 and 49 further in view of Molloy et al. (2003. Sports Med. 33:381-394).

Appellants argue (page 12, 2nd and 3rd paragraph of Appeal Brief) that the references in combination do not teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. Appellants assert one would not be motivated to substitute the thalidomide of Lehman et al into the method of Dunn to arrive at the claimed invention and argue that the state of the art was

not local administration into a joint of an inhibitor of TNF-α synthesis (page 12, 3rd paragraph of Appeal Brief). Thus, one of ordinary skill in the art would not be motivated to combine the teachings of the three references with any reasonable expectation of success in treating an inflamed orthopedic joint by transcapsularly administering an inhibitor of TNF-α synthesis and a growth factor provided by platelet concentration.

It is noted that Appellant has not argued the contribution of Molloy et al. per se.

Appellant's arguments have been fully considered but are not found to be persuasive for reasons stated above and for the following reasons.

The teachings of Lehman et al., and Dunn and the relevance of these teachings to the instant Appeal Brief are disclosed in detail above. Appellants' arguments as to the state of the art at the time of the instant invention are duplicative and are fully addressed above. As noted above, Appellants do not argue the contribution of Molloy et al per se. One would have been motivated to include PDGF in the therapeutic formulation, because of the teachings of Molloy et al that PDGF plays a significant role during early and intermediate stages of healing of intrasynovial tendons, thus contributing to healing of joint injuries and inflammation.

The rejection of Claim 50 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al and Dunn as applied to Claims 1 and 49 further in view of Molloy et al. should be sustained for reasons set forth above.

The rejection of Claims 1, 53 and 57 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Smith et al. (2002, PG PUB US 2002/0169162).

Appellants argue (page 13, 2nd paragraph of Appeal Brief) that none of cited references alone or in combination teach or suggest treating an inflamed orthopedic joint comprising transcapsularly administering an inhibitor of TNF-α synthesis. Smith et al does not teach or suggest administering an inhibitor of TNF-α synthesis (page 13, 3rd paragraph of Appeal Brief). One of ordinary skill in the art would not be motivated to

combine the teachings of the cited references with any reasonable expectation of success in treating an inflamed orthopedic joint.

Appellants' arguments have been fully considered but are not found to be persuasive for the following reasons.

The teachings of Lehman et al. and the relevance of these teachings to the instant Appeal Brief are disclosed in detail above. Lehman et al. teach systemic administration of thalidomide, a compound known to be an inhibitor of TNF-α synthesis for treatment of inflamed joint. Smith et al teaches a method for administering a therapeutically effective compound to the synovial fluid of a joint. Among the agents to be administered by said device are anti-inflammatory drugs. As discussed above, thalidomide (taught by Lehman et al) is an anti-inflammatory agent, since it inhibits the synthesis of TNF-α, a pro-inflammatory protein.

The Examiner does not disagree with appellants that neither Lehman et al nor Smith et al. describes or suggests Appellants' invention. However, Appellants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091,

Appellants argue (page 13, of Appeal Brief, last paragraph bridging page 14, lines 1-3) that one of ordinary skill in the art would not be motivated to combine the teachings of Lehman et al. and Smith et al. with any reasonable expectation of success in treating an inflamed orthopedic joint, by transcapsular administration of an inhibitor of TNF-α synthesis either by synovial fluid or by drug pump. None of the references cited alone or in combination teach or suggest the claimed invention.

Appellants' arguments have been fully considered but are not found to be persuasive for the following reasons.

Appellants have argued the rejection, but the arguments are not supported with specific facts or reasoning. One of ordinary skill in the art would be motivated to modify the teachings of Lehman et al. (as to systemic administration of thalidomide) and administer thalidomide formulations using the methods of drug administration taught by Smith et al. One would be motivated to make these modifications because the art

recognizes the toxic side effects of the systemic use of thalidomide and Smith et al teaches the advantages achieved by an implantable sustained release device for locally administering a therapeutically effective compound, such as an anti-inflammatory drug to synovial fluid of a joint.

The rejection of Claims 1, 53 and 57 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al in view of Smith et al. should be sustained for reasons set forth above.

The rejection of Claim 55 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) and Dunn as applied to Claim 1 in view of Cardone et al (2003, American Family Physician, 67:2147-2152).

Appellants argue (page 14, 2nd full paragraph of Appeal Brief) the three cited references in combination do not teach or suggest treating an inflamed joint comprising transcapsularly administering an inhibitor of TNF-α synthesis. Lehman et al do not teach such a formulation that further comprises a growth factor provided by platelet concentration. Dunn teaches treating an inflamed joint by injecting growth hormone and buffer solution into joint space. Cardone et al teaches aspiration procedures for the knee for the purpose of diagnosing….and to relieve discomfort….; Cardone et al does not teach or suggest removing a portion of the synovial fluid prior to transcapsular administration of an inhibitor of TNF-α synthesis. One would not be motivated to substitute the thalidomide of Lehman et al into the method of Dunn to arrive at the claimed invention. The state of the art was not local administration into a joint of an inhibitor of TNF-α synthesis. One of ordinary skill in the art would not be motivated to combine the teachings of Lehman et al, Dunn and Molloy et al (?) (page 15, 1st paragraph, top of page of Appeal Brief) with any reasonable expectation of success.

Appellant's arguments have been fully considered but are not found to be persuasive for reasons stated above and for the following reasons.

The teachings of Lehman et al., and Dunn and the relevance of these teachings to the instant Appeal Brief are disclosed in detail above. Appellants' arguments as to

the state of the art at the time of the instant invention are duplicative and are fully addressed above.

The Examiner does not disagree with appellants that neither Lehman et al nor Dunn nor Cardone et al. describes or suggests Appellants' invention. However, Appellants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091,

Furthermore, Appellant is arguing limitations not recited in the claims. Claim 55 is dependent from claim 1. The claims are drawn to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering into the joint space a formulation comprising an effective amount of an inhibitor of TNF-α synthesis, wherein a portion of the synovial fluid is removed prior to administration of the inhibitor of TNF-α synthesis. The claims do not recite a formulation that further comprises a growth factor provided by platelet concentration. Additonally, Appellants indicate claims are rejected over the teachings of Lehman et al, Dunn and Molloy et al. This is incorrect: Claim 55 is rejected over Lehman et al and Dunn as applied to Claim 1 in view of Cardone et al.

In response to appellants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine the teachings of Lehman et al. and Dunn and the expectation of success are discussed in detail above. One would be motivated to modify the teachings of Lehman et al. and Dunn and add the step of withdrawing a portion of the synovial fluid prior to administration of the inhibitor of TNF-α synthesis and have a reasonable expectation of success because Cardone et al. teach that aspiration may be performed to aid in diagnosis and relieve discomfort.

Appellants' argue (page 14 of Appeal Brief, 2nd complete paragraph) Cardone et al teaches aspiration procedures for the knee for the purpose of diagnosing an unexplained effusion and to relieve discomfort caused by the effusion, and does not teach or suggest removing a portion of synovial fluid prior to trans-capsular administration of an inhibitor of TNF-α synthesis.

Appellant's arguments have been fully considered but are not found to be persuasive.

The fact that Cardone et al. teaches aspiration procedures for the knee for purposes different than those of instant invention does not overcome the rejection. As stated in MPEP 2144 "It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."). Additionally, a practitioner is always motivated to relieve discomfort.

The rejection of Claim 55 under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al in view of Cardone et al should be sustained for reasons set forth above.

The rejection of Claim 46 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

On page 17, 3rd paragraph, of Appeal Brief, Appellants argue, that while LaVan et al. disclose stability problems with in vivo glucose sensors, the reference does not disclose such problems with inflammatory-responsive delivery system. Appellants assert that Pike et al (PGPUB 20030134792, cited by examiner above) states, at paragraph 0053, that sustained release devices comprising inflammatory-responsive delivery systems are "well known in the art" and can be used to administer a

therapeutically effective dose of an agent directly at the site. Additionally, Appellants assert that enablement does not require reduction to practice or establishment of a particular degree of safety or efficacy.

Appellants' arguments have been fully considered but are not found to be persuasive for the following reasons.

The specification provides no guidance and/or direction or working examples of a sustained release device which could deliver a formulation comprising an effective amount of an inhibitor of TNF-α synthesis to the joint space wherein the sustained release devise comprises an inflammatory-responsive delivery system. LeVan et al is cited to establish that at the time of the instant invention, technological barriers existed to the development of a responsive delivery system which can release therapeutic formulations in response to a pathological condition: "Efforts to miniaturize drug delivery devices…..ultimately promise integrated systems that combine device technology with therapeutic molecules ....to allow the creation of implantable devices that can monitor health status and provide prophylactic or therapeutic treatment in situ. At present, however, these efforts are constrained by …technological barriers." (page 1184, 1st column, 1st paragraph). Thus, the teachings of LeVan et al. are directed to such devices in general, and discuss insulin delivery samples by way of example. Appellants refer to the teachings of Pike et al, specifically paragraph 0053 as indicating sustained release devices comprising inflammatory-responsive delivery systems are "well known in the art". However, Pike et al does not teach anything about an "inflammatory-responsive delivery system". Pike et al teaches sustained-release device or delivery system comprising, for examples, a biodegradable matrix which will allow for sustained release of therapeutic compound such that the level of the compound is maintained at a therapeutically effective level; such a system is enabled. However, claim 46 is directed to an inflammatory responsive delivery system. The teachings of Pike et al do not address "inflammatory-responsive delivery system", that is, a system that releases a therapeutic formulation in response to recognizing the presence of inflammation. Appellant has set forth the standard for enablement with which Examiner takes no

issue. However, the specification does not prevent sufficient guidance as to how to practice the method of the instant invention without resorting to undue experimentation.

The rejection of Claim 49 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

On page 18, 1st full paragraph of Appeal Brief, Appellants argue that specification discusses the (growth) factors in detail. The level of skill in the art is high and therapeutic administration of growth factors was well known in the art at the time of the invention. A skilled practitioner could easily determine whether an inflamed knee joint is being treated, and how to determine appropriate dosage of known factors with only routine experimentation.

Appellants' arguments have been fully considered but are not found to be persuasive for the following reasons:

Appellants' teachings are directed to many different families of growth factors, each comprising a number of member proteins which also comprise numerous subsets of the identified protein families. The art of record recognizes many examples of polypeptide families of growth factors wherein individual members have distinct, and sometimes even opposite, biological activities. The art recognizes that some growth factors, such as TGF-β, IGF-1, and FGF-2, may promote mesenchymal stem cell chondrogenic differentiation in experimental studies; however, these advances are still at the pre-clinical, experimental stage. Appellants' recitation is an invitation to experiment to determine which of the myriad growth factors would be effective to repair joint tissue.

It would require undue experimentation on the part of the artisan to determine which of the myriad of possible growth factors, which have distinct, and often opposite effects, would be effective in repairing joint tissue before one would be able to practice the methods of the instant invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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